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Nearly one million Americans suffer from chronic fatigue syndrome (CFS). More than 15% of Gulf War veterans (GWV) were found to have CFS. The disease significantly reduces work production of civilian patients and combat ability/readiness of US military forces. Increasing scientific evidence suggests that CFS is a biological illness involving pathology of the central nervous system (CNS). However, little is known about how the CNS is affected by CFS. This study will focus on evaluating brain activities of CFS patients during fatigue and non-fatigue muscle exercises. Our hypothesis is that the brain activation pattern in CFS differs from that of healthy controls. Aim 1 of the study is to determine brain activation patterns during motor activity in CFS patients using functional magnetic resonance imaging. Aim 2 is to examine brain activation patterns during motor activity in CFS patients by analyzing signals of electroencephalograms. Aim 3 is to evaluate signal relationships among different brain regions and between the brain and muscle. Measurements will be made from four groups of participants: a civilian CFS group, a civilian control group, a GWV CFS group, and a GWV control group. We expect that the study will provide objective information for diagnosis of CFS.

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Chronic fatigue syndrome, Gulf War Syndrome, functional MRI, electroencephalogram(EEG) Electromyogram(EMG), brain motor activity, brain activation pattern, EEG frequency

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INTRODUCTION

Chronic fatigue syndrome (CFS) is an illness that affects quality of life of both civilian and military populations. However, the diagnosis of CFS is difficult to make because of the absence of specific biomedical markers. Thus, the diagnosis depends primarily on determining whether subjective information provided by the patient meets the clinical case definition of the syndrome. The purpose of this study is to determine whether the central nervous system signals of CFS patients for performing fatigue and non-fatigue motor activities are impaired compared to the signals of healthy volunteers. It is hypothesized that the CNS signals of CFS patients will significantly differ from those of healthy controls. It is expected that at least one or more measurements made by this study will serve as "biological markers" for more objective diagnoses of CFS.

BODY

This report covers the second year of work related to this study. So far, a manuscript based on the results of the analyzed data has been accepted for publication in the journal of *Clinical Neurophysiology*. Further analyses of data collected in the first two years are ongoing and more publications are expected in the future. Work that performed in the second year of the project include:

I. *Recruiting and testing research subjects.* We have collected data from 30 subjects, 16 CFS patients and 14 control subjects. The manuscript to be published soon is based on data from 16 of the 30 subjects.

II. *Developing data analysis software and performing data analysis.* We have developed two software packages for the analysis of electroencephalogram (EEG) and electromyogram (EMG) data. We used these software packages to analysis the collected data and have reported the first set of results in the manuscript to be published. Further and more sophisticated data analysis is underway and we anticipate that the new results will lead additional publications. New data analysis include mapping of the electrical signals recorded from the scalp during motor performance using high-density EEG recordings and characterizing differences in frequency modulation and functional connectivity between the brain and muscle in patients and control subjects when they performed motor tasks that induced fatigue.

KEY RESEARCH ACCOMPLISHMENTS

I. The first set results of the study have been accepted for publication by a high-quality medical and scientific journal (*Clinical Neurophysiology*).

II. Three presentations on the topic of this study have been made at regional, national, and international scientific conferences

REPORTABLE OUTCOMES

I. Motor performance of the CFS patients was poorer than the controls.

II. Relative power of EEG theta frequency band (4-8 Hz) during performing a non-fatigue (NFT) and fatigue (FT) task was significantly greater in the CFS than control group ($P < 0.05$).

III. The amplitude of negative potential (NP), a major component of EEG-derived movement-related cortical potential for the combined NFT and FT tasks was higher in the CFS than control group ($P < 0.05$).

IV. Within the CFS group, the NP was greater for the FT than NFT task ($P < 0.01$), whereas no such difference between the two tasks was found in the control group.

CONCLUSIONS

The results show that chronic fatigue syndrome involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of CFS.

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I. Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clinical Neurophysiology*, accepted.

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ALTERED CENTRAL NERVOUS SYSTEM SIGNAL DURING MOTOR PERFORMANCE IN CHRONIC FATIGUE SYNDROME

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Title Page 2:

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Key words: Motor activity-related cortical potential (MRCP); negative potential (NP); electroencephalography (EEG); electromyography (EMG); voluntary muscle contraction; muscle fatigue; muscle strength.

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Abstract

Objectives: The purpose of this study was to determine whether brain activity of CFS patients during voluntary motor actions differs from that of healthy individuals.

Methods: Eight CFS patients and eight age- and gender-matched healthy volunteers performed isometric handgrip contractions at 50% maximal voluntary contraction level. They first performed 50 contractions with a 10-s rest between adjacent trials – "Non-Fatigue" (NFT) task. Subsequently, the same number of contractions was performed with only a 5-s rest between trials – "Fatigue" (FT) task. Fifty-eight channels of surface EEG were recorded simultaneously from the scalp. Spectrum analysis was performed to estimate power of EEG frequency in different tasks. Motor activity-related cortical potential (MRCP) was derived by triggered averaging of EEG signals associated with the muscle contractions.

Results: Major findings include: (i) Motor performance of the CFS patients was poorer than the controls. (ii) Relative power of EEG theta frequency band (4-8 Hz) during performing the NFT and FT tasks was significantly greater in the CFS than control group ($P < 0.05$). (iii) The amplitude of MRCP negative potential (NP) for the combined NFT and FT tasks was higher in the CFS than control group ($P < 0.05$). (iv) Within the CFS group, the NP was greater for the FT than NFT task ($P < 0.01$), whereas no such difference between the two tasks was found in the control group. **Conclusions:** These clearly show that CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of CFS.

Introduction

The syndrome of chronic fatigue has been described by various terms in the medical literature since the early 17th century. In 1988, the U.S. Centers for Disease Control and Prevention (CDC) proposed a research case definition for chronic fatigue syndrome (CFS) as an illness characterized by an abrupt onset of persistent or relapsing fatigue and other criteria (Holmes *et al.*, 1988). The fatigue in CFS patients is usually described as debilitating or a state of easy fatigability that does not resolve with bed rest, is severe enough to impair average daily activity below 50% of the premorbid level, and lasts for a period of at least 6 months (Gonzalez *et al.*, 1996; Johnson *et al.*, 1999). The fatigue worsens when patients engage in physical activities or muscle exertions (Fukuda *et al.*, 1994; Gonzalez *et al.*, 1996; Johnson *et al.*, 1999). The diagnosis of CFS is difficult to make because of the absence of specific biomedical markers. Thus, the diagnosis depends primarily on determining whether subjective information provided by the patient meets the clinical case definition of the syndrome (Dickinson, 1997; Fukuda *et al.*, 1994; Holmes *et al.*, 1988; Schluederberg *et al.*, 1992).

Several hypotheses have been proposed to outline the etiology and pathology of CFS. One hypothesis is that CFS is a primary affective spectrum disorder, in particular a type of chronic depression (Demitrack, 1994). Others (Zubieta *et al.*, 1994) have suggested that CFS is a persistent immune dysfunction initiated by some infectious process, such as a virus. Demitrack (1994) also proposed that the biological as well as behavioral features of CFS might be linked to endocrine dysfunction of the hypothalamo-pituitary-adrenal axis. In recent

years, increasing scientific evidence has emerged to suggest that CFS is a biological illness involving pathology of the central nervous system (Komaroff, 2000).

A number of studies have shown that the central nervous system in CFS patients is affected by the disorder. Kent-Braun and coworkers (1993) reported that CFS patients have less ability to maximally activate their lower leg muscles, indicating a reduced capacity of brain signal to the working muscle. Post-exercise motor cortical excitability is reduced in CFS patients as compared with healthy volunteers (Samii *et al.*, 1996). Using single photon emission computer tomography (SPECT), researchers found CFS-related perfusion defects in the frontal and temporal lobes (Schwartz *et al.*, 1994a) and impaired cerebral blood flow (Ichise *et al.*, 1992). Magnetic resonance imaging data acquired from CFS patients have shown abnormalities in the white matter signal intensity (Buchwald *et al.*, 1992; Natelson *et al.*, 1993; Schwartz *et al.*, 1994b). Reaction time was slower and amplitude of EEG-derived premovement-related cortical potential reduced in CFS (Gordon *et al.*, 1999). These observations suggest that the central nervous system of CFS patients is altered from the normal state and that the abnormality may be more specific and easier to classify during motor activities that exaggerate the sense of fatigue. However, brain signal changes during muscle exercises that lead to moderate and severe muscle fatigue in CFS have seldom been investigated. None of the previous studies was able to examine motor output, muscle activation, fatigability, and brain signals simultaneously. Recent studies from our laboratory have reported brain activation modulation during low- and high-level motor activity-induced muscle fatigue in healthy volunteers using EEG and functional MRI measurements (Lewandowski *et al.*, 2002; Yao *et al.*, 2002; Liu *et al.*, 2002, 2003). The purpose of this study was to characterize EEG-recorded brain signals in CFS patients and healthy controls

during handgrip exercises involving moderate to relatively high levels of muscle fatigue by simultaneously recording scalp EEG, surface EMG, and mechanical output (force) signals. It was hypothesized that brain signals, whether in the time or frequency domain, or both, of CFS patients would differ from those of healthy controls, and the differences may serve as biological markers for more objective diagnosis of CFS.

Material and Methods

Subjects

Eight medication-free CFS patients (5 men and 3 women, age = 43.1 ± 7.6 years) who met the CDC's criteria for CFS (Holmes et al. 1988) were recruited from the Department of Rheumatic and Immunologic Disease at the Cleveland Clinic. (The patients were medication free on and at least 10 days prior to the experiment day). All patients were free of neuromuscular and active mood disorders. They were given a detailed history review and physical examination and were screened for active and past psychiatric disease by clinical interview and for clinical depression with the Beck Depression Index. More detailed patient information is given in Table 1. Eight age-matched, sedentary healthy individuals were recruited and served as control subjects (5 men and 3 women, age = 42.3 ± 8.2 years). All individuals were right-handed as determined by the Edinburgh inventory (Oldfield, 1971). The Institutional Review Board at the Cleveland Clinic Foundation approved the study, and all subjects gave informed consent prior to their participation.

Motor tasks

All subjects performed two motor tasks with the right hand: "non-fatigue" (NFT) and "fatigue" (FT). The NFT task consisted of 50 handgrip contractions at 50% maximal voluntary contraction (MVC) level. Each contraction lasted ~1 s with a 10-s rest between each two consecutive trials. The fatigue task consisted of 50 repetitions of the same handgrip activity but with only a 5-s rest between trials. Before each trial, a soft beep generatd by a digital stimulator and a speaker signaled the time for the subject to begin the contraction. The NFT task was performed first followed by a 30-s rest and then the FT task. Handgrip force, electromyographic signals (EMG) and electroencephalograms (EEG) were recorded when subjects performed the motor tasks.

Force recording

Subjects were seated comfortably in an experimental chair in a shielded data-recording room. The handgrip force was recorded using a custom-built computerized force measurement system (Fig. 1A). The system consisted of a handgrip device connected to a pressure transducer (EPX-N1 250, Entran Devices, Fairfield, NJ) through a nylon tube (3 mm diameter) filled with distilled water. The right forearm rested on a padded support at hip height in an intermediate position between supination and pronation of the forearm. An oscilloscope (Tektronics TDS240) was located about 3 ft in front of the subject with a target line on the screen indicating the target force (50% MVC force). Subjects were instructed to reach the target line by gripping the handgrip device with a comfortable rate. The force (pressure) signal was converted to voltage by the pressure transducer, digitized (250 samples/s) via a NeuroSoft system (Neuroscan, El Paso, TX), and saved on the hard disk of a personal computer.

EEG recording

EEG signals were recorded from the scalp using a 64-channel NeuroSoft SYNAMPS system (Neuroscan, El Paso, TX). Six electrodes were not used, resulting in recording 58 channels of EEG data. The EEG electrodes were fixed on an elastic QuickCap nylon cap, which was applied to the subject's head. The electrode positioning on the cap was based on the International 10-20 method (Jasper, 1958) and some basic placements defined by Chatrian et al. (1985). All the electrodes were referenced to the linked mastoids (left and right). After the electrode cap application, conducting gel (Electro-gel^{TM}, Electro-Cap International, Inc., Eaton, OH) was injected into each electrode to connect the recording surface of the electrode with the scalp. An impedance map of the electrodes was displayed on the monitor of a personal computer, in which the data acquisition software is stored. Impedance of the electrodes was adjusted by injecting additional gel or applying additional pressure to the electrode and maintained below 10 kΩ. The EEG signals were amplified (X75,000), bandpass filtered (0.03 to 50 Hz), and digitized (250 samples/s), and stored on the hard disk of the computer.

EMG recording

Surface EMG signals were recorded from the first dorsal interosseous (FDI), flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS) and extensor digitorum (ED) muscles as well as from the contralateral (left) FDP. The muscles were identified by palpating the skin when subjects made appropriate finger movements. The electrode placement for the FDP muscle was 1-2 cm medial to the ulnar bone and 3-5 cm distal to the

elbow joint. Bipolar electrodes (8 mm recording diameter) were located on skin overlying each muscle with a ~2 cm inter-electrode distance. Before the electrode application, the skin was cleaned with alcohol wipes. The EMG signals were amplified (X1000), band-pass filtered (10-1000 Hz), digitized (2000 samples/s), and saved on the hard disk of the personal computer.

Experimental procedures

Each subject was briefly trained before the experiment to correctly perform the tasks. Visual feedback was provided on the oscilloscope to ensure that the target level was reached and the rate of rise of force was consistent. A 2-min baseline EEG *(B1)* was then recorded, during which subjects rested. After that, three trials of handgrip MVC *(MVC1)* were performed to obtain the maximal value of the handgrip force and finger flexor muscle EMG. The maximal EMG values of the FDI, ED, and the left side FDP were also obtained by making MVCs of the index finger abduction, finger extension, and finger flexion of the left hand, respectively. These MVC EMG values were later used for the normalization of the corresponding EMG values during the task performance.

Based on the handgrip MVC force (maximal value of the 3 MVC trials), the 50% target force was determined and displayed by a target line on the oscilloscope. Fifty trials of the non-fatigue *(NFT)* task were performed followed by a 30-s rest before performing the 50 trials of the fatigue *(FT)* task. For each trial, when the handgrip force reached 5% MVC level, a trigger signal was generated and stored in a separate channel in the data file. These trigger signals associated with the NFT and FT handgrip contractions were later used to perform triggered averaging of the EEG signals. Subjects were told not to blink or move their eyes,

not to bite down with their teeth or tense the facial or neck muscles, as these activities would create "noise" in the EEG signals. These activities, however, were allowed during the inter-trial interval; in which the EEG signal was not used for the data analysis (see below). Immediately after completing the FT task, three trials of MVC *(MVC2)* were performed. Finally, a second period (2 min) baseline EEG *(B2)* was collected with the subject rested. The experimental paradigm is presented in Fig. 1B.

Data analysis

EEG frequency analysis. NeuroSoft-Edit data analysis software (Neuroscan, El Paso, TX) was used for EEG analysis. All EEG signals were visually inspected to remove artifacts associated with eye blinks or other activities that induced noises. Spectral analysis using fast Fourier transform (FFT) was performed on raw EEG data of each subject associated with B1, MVC1, NFT, FT, MVC2, and B2 events. For B1 or B2, 30 noise-free EEG epochs were analyzed. For MVC1 or MVC2, three EEG epochs associated with 3 MVC trials were analyzed. For the NFT or FT task, 40 noise-free EEG epochs associated with 40 trials were selected. Each epoch contained 512 data points (2048 ms). For the epochs associated with the NFT and FT tasks, the last EEG data point in each epoch was aligned with the timing of 5% handgrip MVC force (trigger point, see below); thus, the EEG epoch covered the time period involved with preparation and execution activities of the cortex.

For each epoch, a power spectrum (expressed as μV^2) was calculated, and the power for each of the following standard EEG frequency bands was derived: delta (0.5-4 Hz), theta 4-8 Hz), alpha1 (8-11 Hz), alpha2 (11-14 Hz), beta1 (14-25 Hz), and beta2 (25-35 Hz). Relative power of each band as a percentage of the total power was calculated. Subsequently,

the mean relative power of each band across the number of epochs (e.g., 40 epochs for the NFT task) was obtained. The above analysis was performed for each of the 58 electrodes, an average of relative power based on all electrodes for each frequency band, and task in each subject was determined. Finally, based on the averages of data from each individual subject, a grand average of relative power was obtained for each frequency band and task in each group.

EEG amplitude analysis. Each handgrip contraction triggered a 1500-ms window of EEG (1000 ms before and 500 ms after the trigger). A triggered averaging over all the EEG windows corresponding to all the NFT or FT trials was obtained. The triggered averaging is termed motor activity-related cortical potential (MRCP) because it was time-locked with each handgrip muscle contraction. With this time-locked triggered averaging, random signals irrelevant to the motor task were averaged out; only those signals directly related to the controlling of the handgrip contraction (MRCP) were retained. The amplitude of MRCP was measured from the baseline (B1) to the peak of the negative potential (NP). The baseline value was determined by taking the mean value of the B1 epoch (2 min). This NP (B1 to peak) represents cortical activity directly related to planning and execution of a motor action (Fang *et al.*, 2001; Hallet, 1994; Siemionow *et al.*, 2000). A group average of the NP amplitude associated with the NFT and a group MRCP average associated with the FT tasks were determined after the triggered averaging was performed in each subject.

EMG analysis. The EMG signals of each muscle of each trial were rectified and averaged over a 500-ms period starting from the trigger. An average over all trials in each muscle for each task in each subject was then calculated. This average EMG was normalized

to the MVC EMG measured at the beginning of the experiment. Finally, a group average of the normalized EMG was determined.

Force analysis. The handgrip force was measured at the peak of the recorded force in each trial. An average peak force for each task for each subject was then calculated. The average peak force was normalized to the peak force of MVC1. A group average of the normalized NFT force and a group average of the normalized FT force were determined.

Statistical analysis

MRCP NP, relative power EEG frequency, EMG, and force were compared between the tasks and between the CFS and control groups. Due to the repeated nature of the measurements, a two-way repeated measures analysis of variance (ANOVA) model was used. The two independent factors were group (patients vs. control) and task (e.g., NF vs. FT). The analyses were performed using the Prism 2.01 statistical program (GraphPad Software, Inc., San Diego, CA). Separate 2-way ANOVA analysis was performed for each dependent variable (relative power of frequency, MRCP NP, EMG, or force). For the NP data, only those channels or recording locations showing significant MRCP were included in the analysis. This means that although 58 channels EEG were recorded, not all 58 channels of MRCP NP data were analyzed. Each channel of NP and EMG of each muscle was analyzed separately. A significance level of $P \leq 0.05$ was used for all statistical analyses. All data in the text were presented as means ± standard deviations (mean ± SD).

Results

Force

MVC force. The MVC handgrip force (MVC1) of the CFS group (305.8 ± 150.4 N) was significantly lower ($P < 0.02$) than the MVC force of the control group (412.0 ± 103.6 N). At the completion of the experiment (the end of the FT task), the MVC force (MVC2) reduced to 252.6 ± 136.4 N (83% of the MVC1 value) for the CFS group and to 374.6 ± 96.4 N (91% of the MVC1 value) for the control group (Fig. 2A). The decline in the MVC force was significant for the CFS patients ($P < 0.05$) but insignificant for the control group ($P > 0.1$). These results indicate that (i) although the two groups were age-, gender-, height-, and weight-matched, the CFS patients were weaker than the healthy subjects; and (ii) the CFS patients fatigued significantly whereas the healthy controls did not. This was demonstrated by a greater loss in the MVC force (MVC2) in the patients after performing the two motor tasks (Fig. 2A).

NFT and FT task forces. For the NFT task, both groups overshot the 50% target level to a similar extent (Fig. 2B). The actual force exerted by the CFS group for the NFT task was 51.25 ± 6.56% and that exerted by the control group was 51.42 ± 2.29%. For the FT task, although the subjects were told to match the same target level (50% MVC1 force), the CFS patients failed to reach the target force (48.88 ± 7.45%), whereas the control group still overshot the target (50.98 ± 3.81%). Compared with the exerted force during the NFT task, the force exerted during the FT task declined significantly (87% initial value, $P < 0.01$) for the CFS group, but the change in force for the control group was small (96% initial value, $P > 0.1$). The NFT and FT force results again suggest that the CFS patients were more severely fatigued by the motor tasks, especially by the FT task.

EMG

The normalized surface EMG values for the NFT task for the CFS group were 25.4 ± 8.9%, 24.3 ± 2.4%, 38.8 ± 10.8%, 11.2 ± 2.4%, and 3.6 ± 1.1% MVC for the FDI, FDP, FDS, EDC and left FDP muscles, respectively. The EMG values for the FT task for the CFS group were 23.6 ± 7.9%, 23.7 ± 3.8%, 37.9 ± 10.8%, 11.2 ± 1.9%, and 3.1 ± 1.4% MVC for FDI, FDP, FDS, ED, and left FDP muscles, respectively (Fig. 3A).

The normalized surface EMG values for the NFT task for the control group were 22.1 ± 4.3%, 26.4 ± 5.5%, 40.4 ± 7.8%, 11.0 ± 1.9%, and 3.9 ± 1.4% MVC for the FDI, FDP, FDS, EDC, and left FDP muscles, respectively. The EMG values for the FT task for the control group were 23.5 ± 6.4%, 24.7 ± 5.2%, 39.3 ± 6.7%, 12.0 ± 1.7%, and 3.5±1.6% MVC for the FDI, FDP, FDS, ED, and left FDP muscles, respectively (Fig. 3B). No significant differences in EMG were found between the groups or between the two tasks.

Power of EEG frequency

Delta and theta. For the delta band, the relative power of frequency increased from B1 to MVC1 to NFT and FT, and then declined from FT to MVC2 to B2 for both the CFS and control groups. There were no statistically significant differences in the relative power between the two groups (Fig. 4A). In general, the relative power of the theta band in the control group showed a steady *decrease* from B1 to MVC2 (except at FT) and then followed an abrupt increase from MVC2 to B2. On the contrary, the pattern of the power changes in the theta band in the CFS group showed a steady *increase* from B1 to FT followed a decrease

from FT to MVC2 and an increase from MVC2 to B2 (Fig. 4B). The relative power of the theta band in the CFS group was significantly ($P < 0.05$) different from that in the control group at NFT, FT, MVC2, and B2. For the NFT, FT, and MVC2 tasks, the theta relative power of the CFS group exhibited a significant increase from that of the control group, whereas the B2 relative power became significantly lower in the CFS than in the control group (Fig. 4B). Figure 5 shows power maps of theta frequency based on the signals of the 58 electrodes during the NFT task. Each map was derived from the maps of eight subjects (A, CFS patients; B, control subjects). The maps show that the power of the theta frequency during performance of the NFT task was greater in CFS than control subjects (a larger number of electrodes showing higher power in CFS subjects).

Alpha1, alpha2, beta1, and beta2. For the bands of alpha1 and alpha2, the relative power decreased from B1 to MVC1 to NFT and FT, and then the power values recovered to the B1 level from FT to MVC2 to B2. No significant differences in the relative power occurred between the two groups (Fig. 4C). The relative power for the beta1 and beta2 bands showed similar V-shape changes across the tasks for both the groups except that at B2 the relative power for both the beta1 and beta2 bands was significantly higher for the CFS than for the control group (Fig. 4D).

Motor activity-related cortical potential

We chose to quantify the MRCP NP from three electrode locations: Cz, overlying the supplementary motor area, C3 and C4 overlying the primary sensorimotor area contralateral and ipsilateral to the performing (right) limb respectively. The three locations showed prominent MRCP waveforms given the significant involvement of the underlying cortical

fields (primary sensorimotor cortex [C3, C4] and supplementary motor area [Cz]). An example of the NP measurement is given in Fig. 6, which shows that the amplitude of the NP from the Cz location in a CFS patient was higher for the FT task (4.3 μV) than that for the NFT task (3.6 μV).

CFS group. At the Cz recording location, the NP amplitude for the NFT task was 3.5 ± 1.1 μV and that for the FT task was 4.4 ± 1.5 μV. At the C3 recording location, the NP amplitude was 2.5 ± 1.4 μV for the NFT task and 3.5 ± 1.6 μV for the FT task. At the C4 location, the NP amplitude was 2.2 ± 1.7 μV for the NFT task and 3.0 ± 2.4 μV for the FT task. At all three electrode locations, the MRCP increased significantly when the patients performed the FT task compared with when they performed the NFT task ($P < 0.01$). Fig. 7 presents the values from the Cz and C3 electrode locations.

Control group. At the Cz recording location, the NP amplitude for the NFT task was 3.1 ± 0.5 μV and that for the FT task was 3.8 ± 1.2 μV ($P > 0.05$). At the C3 recording location, the MRCP NP amplitude was 2.2 ± 0.9 μV for the NFT task and 2.8 ± 1.4 μV for the FT task ($P > 0.05$). At the C4 recording location, the MRCP NP amplitude was 2.1 ± 0.8 μV for the NFT task and 2.6 ± 1.3 μV for the FT task ($P > 0.05$). The changes in the NP amplitude from the NFT to the FT task were not significant at all three electrode locations.

Between groups. At all three electrode locations, the amplitude of the NP was significantly greater ($P < 0.05$) in the CFS group compared with the value of the control group when the NP data of the NFT and FT tasks were pooled together. The values were similar ($P > 0.05$) (see Fig. 7 for the data from the Cz and C3).

Discussion

The primary goal of this study was to determine whether brain signals of chronic fatigue syndrome (CFS) patients for controlling handgrip motor actions are different from those of healthy individuals. The main findings are: (1) CFS patients exhibited a reduced ability to perform the motor tasks, especially the ones that required maximum exertion of the muscles and that caused greater fatigue; (2) the relative power of frequency of the brain signals (EEG) during performing the motor tasks in the CFS patients was altered from that of the healthy controls; and (3) the magnitude of the control signal (MRCP NP) was greater in the CFS patients than in the healthy controls, indicating that stronger voluntary efforts were needed to perform the same motor tasks.

Motor performance

Strength. The handgrip strength of the CFS patients was significantly (26%) lower than that of the controls. This seems to be a reasonable finding, given that CFS patients are less active during daily living. It is expected that when muscles are less frequently used (such as in CFS patients), both the muscles themselves and the nervous system that supplies them degenerate (as muscle atrophy and an impairment in the ability to fully activate muscles seem to attest), leading to strength losses (Yue *et al.*, 1997). A few studies have reported significantly lower strength in CFS patients than healthy controls (Lawrie *et al.*, 2000; Paul *et al.*, 1999). Others, however, have shown that motor function, including muscle strength, is not affected by CFS (Lloyd *et al.*, 1991; Gibson *et al.*, 1993). The discrepancy among these studies regarding voluntary muscle strength in individuals with CFS may be due to different muscle groups tested and/or the severity of the disease in the tested patients.

Fatigability. The CFS patients exhibited higher fatigability or reduced fatigue resistance. This was demonstrated by a substantial decline in maximal handgrip force from MVC1 to MVC2 (Fig. 2A). The MVC2 force of the control group was not significantly changed. When fatigue occurs, muscles' ability to generate force declines, leading to strength losses (review: Enoka and Stuart, 1992). Another indication of greater fatigability in CFS is the difference in average force between the NFT and FT tasks. In the CFS patients, the average FT force was significantly lower than the average NFT force. This result suggests that the patients had fatigued significantly before the completion of the FT task. They could not reach the target level even with the maximal effort. In contrast, the average forces between the NFT and FT tasks in the control group were similar (Fig. 2B), indicating that fatigue was not as apparent in this group as in the CFS group. The increased fatigability in CFS may be a result of reduced use-related changes in muscle property. Numerous studies have shown that when regular use of muscles is significantly reduced (such as in limb immobilization), slow-twitch, fatigue-resistant muscle fibers or motor units are most affected (Edgerton *et al.*, 1975; Haida *et al.*, 1989; Maier *et al.*, 1972, 1976; Nordstrom *et al.*, 1995). It is highly likely that slow-twitch fibers of limb muscles in CFS are similarly influenced by reduced daily use in CFS patients, leading to a decline in resistance to muscle fatigue.

Power of EEG frequency

One of the most significant findings of this study is the substantially greater relative power of the EEG theta frequency on a number of occasions in the CFS patients. The power was similar between the CFS and controls groups for B1 and MVC1 data but differed substantially as soon as the NFT task was performed. This difference was maintained during

the performances of FT and MVC2 tasks, in which the power was greater for the CFS than control subjects (Fig. 4B). In general, the relative power of the theta band showed a declining trend from baseline (B1) to times of motor performance in the control group. In contrast, the relativ power for CFS patients increased steadily from B1 to MVC1 and NFT and then decreased from NFT to FT. For both groups, the power returned to the B1 level at B2 with the control subjects overshot the B1 value (Fig. 4B). It seems that a short period of exercise, such as MVC1 (3 MVC trials), does not make a difference in the power between the two groups. However, 50 trials of handgrip contractions at 50% maximal level made a significant difference in the power of the theta frequency. Further increasing the amount of exercise (subsequent FT and MVC2 muscle activities) did not widen the difference in the relative power of the theta frequency between the two groups. These data suggest that the departure of the relative power of the theta frequency in CFS from the normal value results from a moderate amount of muscle exercise and this departure may serve as a marker for diagnostic purposes.

MRCP

The MRCP NP amplitude for both Cz and C3 locations was greater in CFS than control subjects when the NP results were pooled from the NFT and FT tasks. In the CFS group, the NP amplitude increased to a significantly higher level as the patients shifted from the NFT task to the FT task. These findings indicate that in general, the patients needed stronger voluntary effort to perform the motor tasks; they particularly needed even greater effort to perform a more fatiguing motor task. Many studies have reported increased perceived effort in CFS patients than in healthy individuals in performing motor tasks

(Blackwood *et al.*, 1998; Gibson *et al.*, 1993; Sacco *et al.*, 1999). Previous research has shown a proportional relationship between the amplitude of MRCP NP or other forms of cortical signal measurements and voluntary effort (Dai *et al.*, 2001; Dettmers *et al.*, 1995; Siemionow *et al.*, 2000) and MRCP NP is a sensitive measure to distinguish differences in the amplitude of central command for different motor tasks (Fang *et al.*, 2001; Yue *et al.*, 2000).

The MRCP NP data in the current study are the first to show that cortical signals representing voluntary effort for voluntary motor performance are greater in CFS. Based on the force data that the muscles were more severely fatigued in the CFS than control subjects (force was below target even with maximal effort, Fig. 2), it is reasonable to expect a higher level of voluntary-command signal for the ongoing motor task. This higher level of cortical signal related to controlling the motor task might have reflected a greater effort to recruit additional motor units to compensate for losses of force-generating capability of the muscles or to disinhibit the motor neurons whose activities might have been suppressed by inhibitory inputs from group III and IV aferents that are particularly active during muscle fatigue (Garland *et al.*, 1988, 1991; Hayward *et al.*, 1988, 1991). Based on the results of this study, however, it is not clear whether increased MRCP NP amplitude indicates impairments in the peripheral neuromuscular system or CNS.

Very few studies have investigated cortical signal changes during voluntary motor activities in CFS. Gordon *et al.* (1999) reported a reduction in pre-movement readiness potential in CFS patients compared with healthy individuals. Because readiness potential represents brain activities associated with attention, concentration, and early preparation for the upcoming motor action, this reduction in readiness potential may reflect a reduced ability

in CFS patients to focus their attention and prepare for the muscle action (Prasher *et al.*, 1990).

Conclusions

This study systematically examined EEG-measured brain signals during non-fatigue and fatigue voluntary motor tasks, and other activities in CFS patients and healthy volunteers. The results suggest that CFS patients are weaker and more easily fatigued than healthy individuals are. The relative power of the EEG theta band frequency in the CFS group is significantly greater after a moderate level of muscle exercise than that in the control group. A significantly higher level of cortical activation is needed for CFS patients to perform fatigue than non-fatigue tasks. Compared with healthy controls, CFS patients need greater effort to perform the two motor tasks. These results support the notion that CFS involves altered central nervous system signal in controlling voluntary muscle actions. One or all of these abnormalities (reduced motor-performance ability, increased power of the theta frequency, and greater voluntary effort needed for motor performance) may serve as biological markers for more objective diagnosis of CFS.

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Table 1. Characteristics of CFS and healthy control subjects (Ctrl)

	CFS		Ctrl	
	Male	Female	Male	Female
Age (years)	42.2	46.2	41.2	44.4
Illness onset age (years)	33.2	35.9	-	-
Duration of illness (mo.)	100.8	141.6	-	-
Height (cm)	172.6	163.2	174.3	164.8
Body weight (kg)	83.5	72.5	79.2	68.6

FIGURE LEGENDS

Fig. 1. (**A**) Experimental setting. A pressure transducer system was used for measurement of handgrip force. Scalp EEG was recorded via a 58-channel electrode cap. Surface EMG from the upper extremity locations was measured simultaneously. (**B**) Experimental paradigm. B1 - first baseline period, MVC1 – three trials of maximal voluntary contraction (MVC) measured before the NFT and FT task, NFT - non-fatigue task (50 contractions at 50% MVC with a 10-s rest between trials), FT - fatiguing task (50 contractions at 50% MVC with a 5-s rest between trials), MVC2 - three trials of MVC performed after the FT task, and B2 - second baseline period.

Fig. 2. Handgrip force measurements. (**A**) Force values of MVC1 and MVC2 for the CFS and control (Ctrl) groups. The CFS patients were significantly weaker than the control subjects (MVC1 values). In addition, the MVC2 force declined significantly compared with that of MVC1 in the CFS group, whereas the force values of MVC1 and MVC2 in the control group were similar. (**B**) Mean relative forces (normalized to MVC1 force) for NFT and FT tasks in the two groups. The FT force of the CFS patients dropped significantly from the target line (50% MVC1 level), whereas that of the control subjects did not. Significant declines in MVC2 and FT forces in the CFS group suggest that the patients fatigued more significantly compared with the control subjects. $*P < 0.05$, $**P < 0.01$.

Fig. 3. Normalized surface EMG (relative to MVC1 value). (**A**) Mean EMG values of the NFT and FT tasks for the first dorsal interosseous (FDI), flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS), extensor digitorum communis (EDC), and flexor digitorum profundus in the contralateral (left) arm (FDPc) in the CFS

group. (**B**) Mean EMG values of the NFT and FT tasks for the FDI, FDP, FDS, EDC, and FDPc in the control group. No differences in the normalized EMG values were observed either between the two tasks within each group or in a given task between the two groups.

Fig. 4. Relative EEG power of delta band (**A**), theta band (**B**), alpha band (**C**), and beta band (**D**) for B1, MVC1, NFT, FT, MVC2, and B2 tasks. Total power of all bands for a given task is 100%. For delta, alpha1, alpha2, and a majority of data points of the beta1 and beta2 frequency bands, the relative power changes from one task to another were similar between the CFS and control groups. Significant differences in the relative power were observed at NFT, FT, MVC2, and B2 tasks in theta band (4-8 Hz) between the two groups. For the beta band (14-35 Hz), significant relative power differences between the two groups were observed at B2. $*P < 0.05$.

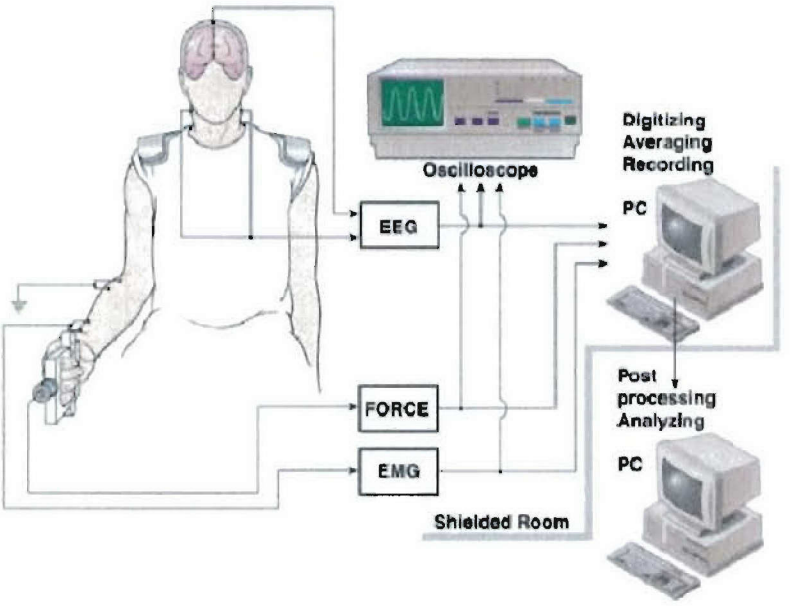
Fig. 5. Power of frequency (theta band) maps expressed as raw power (μV^2, color bar on the right) of the CFS and control groups. Each map is a grand average of individual maps of eight subjects in the group. The maps show that higher power is distributed at a larger area (a larger number of electrodes) in CFS subjects than in control subjects. Each map was derived from signals of 58 electrodes.

Fig. 6. Motor activity-related cortical potential (MRCP) of a CFS patient derived from NFT and FT handgrip contractions. Vertical lines indicate the timing of trigger. The amplitude of the MRCP negative potential (NP) was substantially greater for the FT (4.26 μV) than NFT (3.57 μV) task, although the patient had great difficulty maintaining the FT target force (target force: 50% MVC1, actual force: 42.3% MVC1). For both the NFT and FT MRCP, the upper horizontal line indicates the peak

of the NP and the lower horizontal line depicts the mean of B1 (baseline 1) epoch (2min). The MRCP was from the Cz electrode, located approximately above the supplementary motor area.

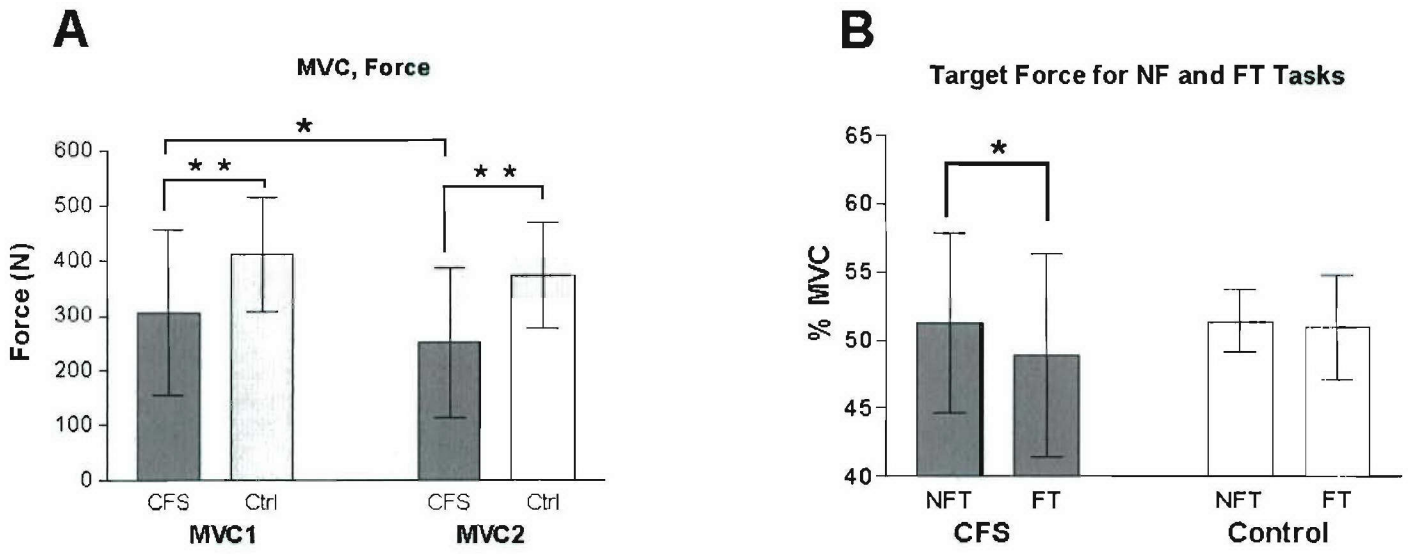
Fig. 7. Group MRCP NP data from Cz (SMA) and C3 (contralateral sensorimotor) locations for the NFT and FT motor tasks. For both the Cz and C3 electrodes, the amplitude of NP in the CFS group was significantly greater than that of the control group when the NP data of the two tasks (NFT and FT) were pooled together. In the CFS group, the NP amplitude grew significantly higher from the NFT task to the FT task. There was a similar trend toward higher NP for the FT than NFT task in the control group, but the difference was not significant. The MRCP NP data suggest that, in general, CFS patients need greater effort to perform motor tasks, and even greater efforts to perform fatigue motor tasks.

A


Oscilloscope
Digitizing
Averaging
Recording
PC
EEG
FORCE
EMG
Post
processing
Analyzing
PC
Shielded Room

B


B1
MVC1
NFT
Rest 30 s
FT
MVC2
B2


A
MVC, Force
Force (N)
600
500
400
300
200
100
0
*
* *
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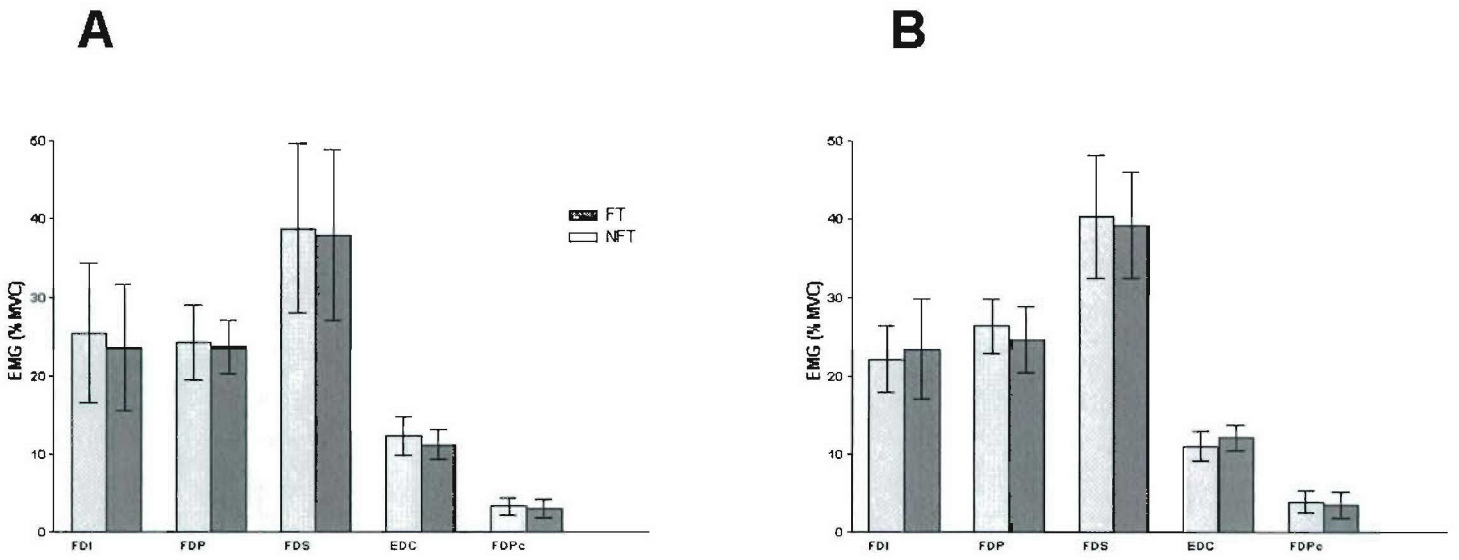
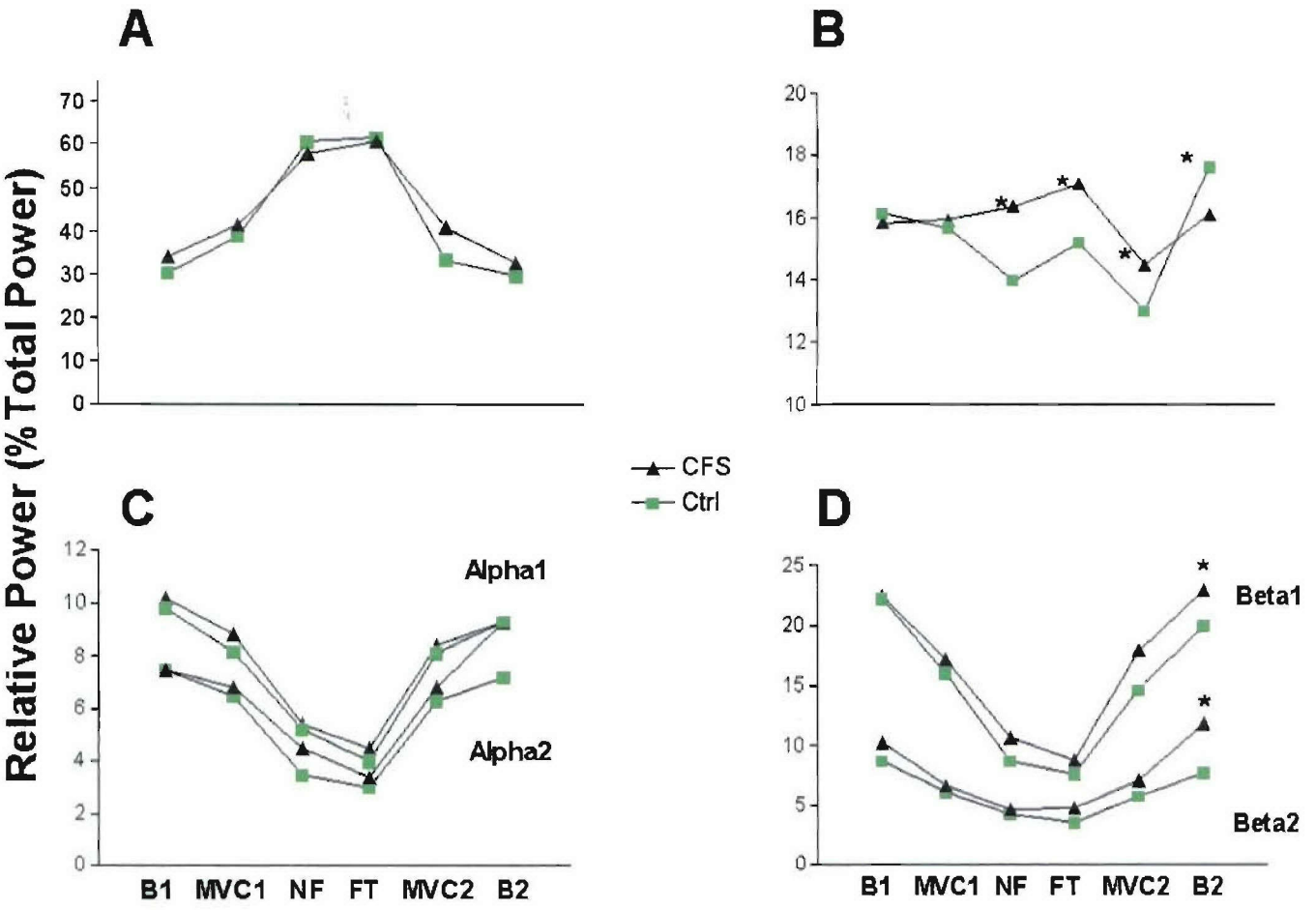
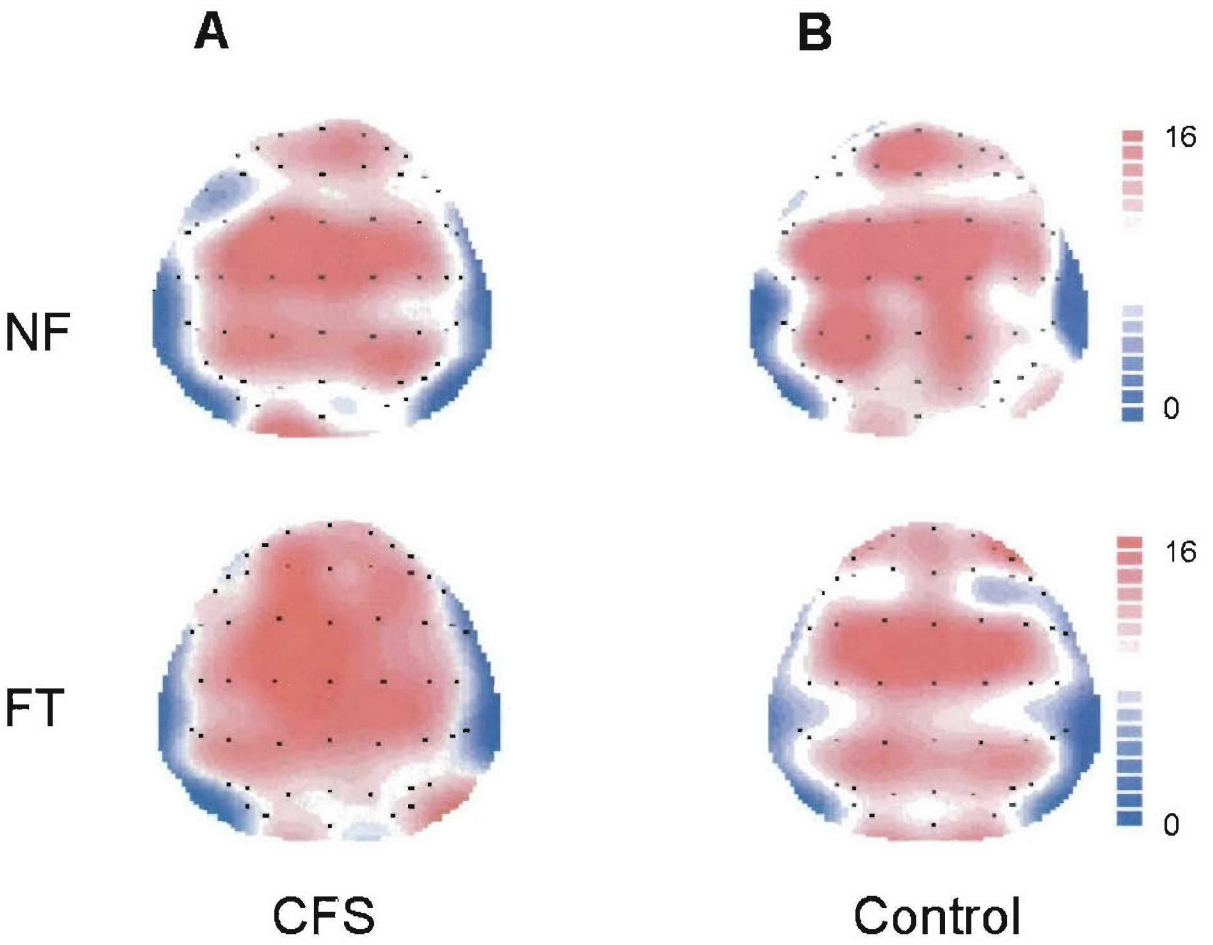
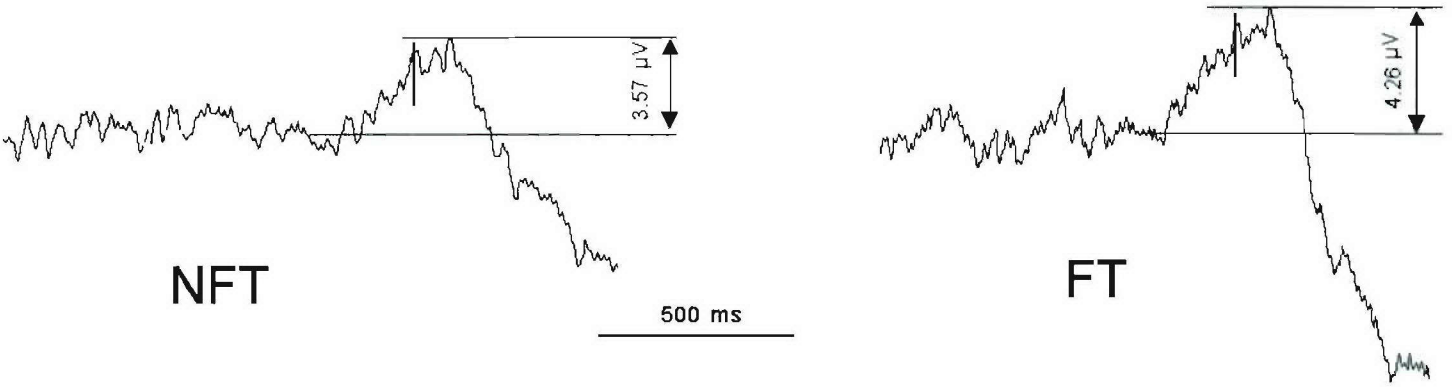
CFS
Ctrl
CFS
Ctrl
MVC1
MVC2
B
Target Force for NF and FT Tasks
% MVC
65
60
55
50
45
40
*
NFT
FT
NFT
FT
CFS
Control

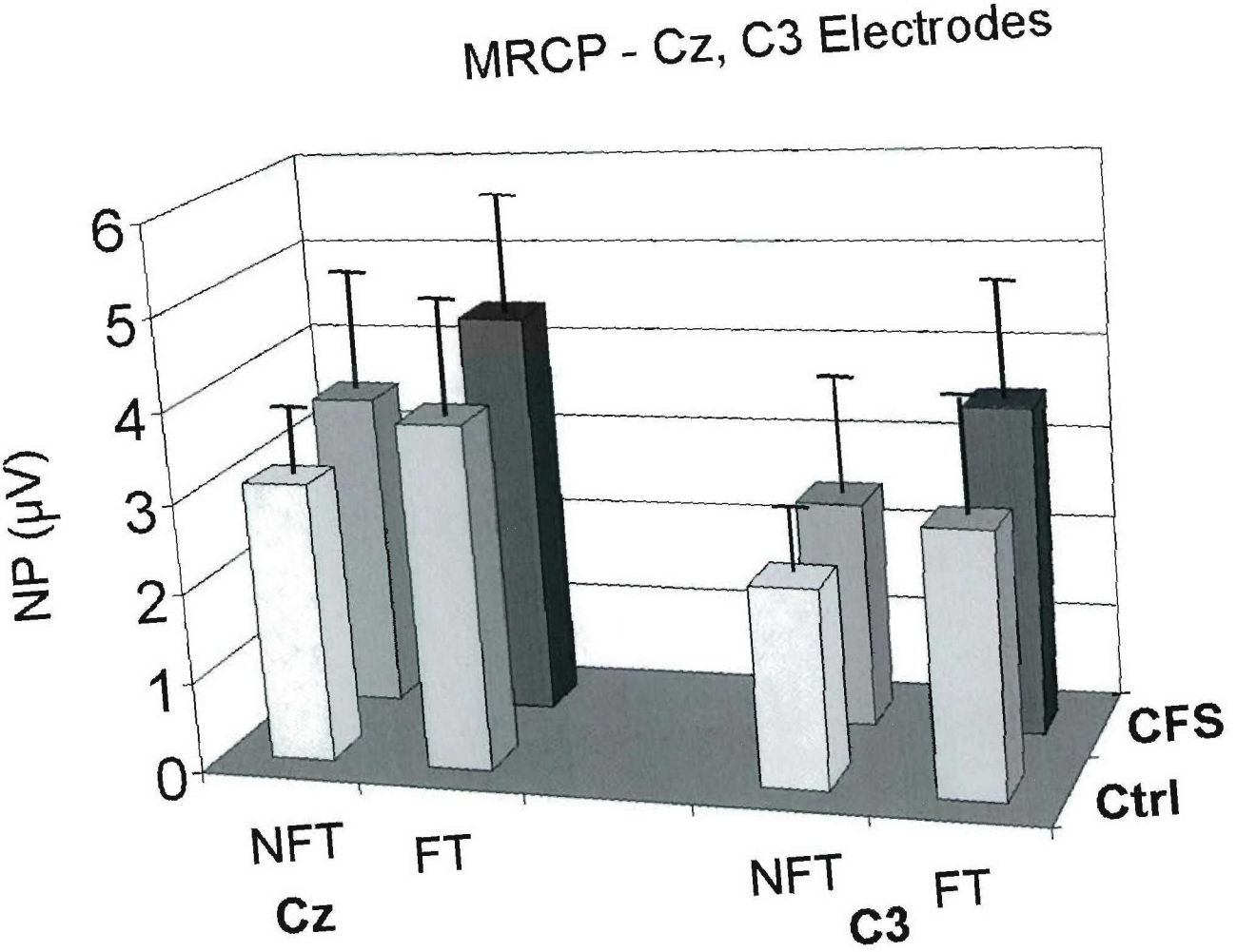

A
B
EMG (% MVC)
0
10
20
30
40
50
FT
NFT
FDI
FDP
FDS
EDC
FDPc


A
B
C
D
Relative Power (% Total Power)
CFS
Ctrl
Alpha1
Alpha2
Beta1
Beta2
B1
MVC1
NF
FT
MVC2
B2


A
B
NF
FT
16
0
16
0
CFS
Control

Motor Related Cortical Potential (MRCP)




MRCP - Cz, C3 Electrodes
NP (μV)
6
5
4
3
2
1
0
NFT
FT
Cz
NFT
FT
C3
CFS
Ctrl